Rejection under 35 U.S.C. §101

The Office Action rejected Claims 31-44 under 35 U.S.C. § 101 for the reasons of record. In particular, the Office Action asserts:

> There is no doubt that certain receptor tyrosine kinase genes are causally associated with certain types of cancers. However, there is no evidence that the receptor tyrosine kinase of the instant invention is associated in any way with any particular type of cancer of with cancers in general.

Applicants respectfully traverse the rejection.

Applicants respectfully submit that the present disclosure provides a specific, substantial and credible utility for the claimed invention. In particular, on pages 95-96 of the specification, the expression of HPTK6 was characterized by Northern blot hybridization of polyadenylated RNA isolated from human tissues. In the human adult tissues, the highest amount of hybridization was detected in samples of RNA from the kidney and placenta (see page 95, lines 26-28). Lower expression was observed in the brain, lung, skeletal muscle, and pancreas (see page 95, lines 28-30). However, no expression in the liver was detected (see page 95, line 30 and Figure 10A). Similar results were obtained in fetal human tissue, as is evidenced in Figure 10B. The highest expression was observed in the fetal brain with lower expression in the fetal kidney and lung tissue (see page 95, line 33 to page 96, line 1). As in the adult tissue, no expression in the liver was detected (see page 96, lines 3-4). Expression of HPTK6 in various cell lines was also studied via Northern blotting of mRNA samples from the cell lines. As shown in Table 3 of page 96, in lines 27-28, a moderate to weak detection of HPTK6 was found in Hep 3B cells, a liver carcinoma. Thus, it is clear that there is a substantial, credible, and specific utility for HPTK6, namely the detection and treatment of liver cancer by HPTK6 by using HPTK6 antibodies, antisense, etc. In addition, Applicants respectfully note that HPTK6 is also expressed

in breast carcinoma cells (e.g., MCF 7), thereby indicating a possible detection and treatment of breast cancer as well. (See page 96, lines 20-22).

Thus, based on the disclosure in the specification, it is clear that the isolated nucleic acid molecules encoding an HPTK6 receptor such as the nucleic acid molecules claimed in the present application have a credible, substantial, and specific utility. Accordingly, reconsideration and withdrawal of the rejection of Claims 31-44 under 35 U.S.C. §101 are respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph

The Office Action rejected Claims 31-44 under 35 U.S.C. §112, first paragraph as failing to adequately teach how to use the instant invention for those reasons given in the rejection under 35 U.S.C. §101 set forth above.

Applicants respectfully traverse the rejection.

A deficiency under 35 U.S.C. §101 also creates a deficiency under 35 U.S.C. §112, first paragraph. In re Brana, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); In re Kirk, 376 F.2d 936, 942, 153 USPQ 48, 53 (CCPA 1967). Thus, in order to be enabled, a claim must be supported by a disclosure showing practical utility. As discussed above, the present disclosure provides a specific, substantial and credible utility for the claimed invention. Thus, the claimed invention meets the requirements of 35 U.S.C. §112, first paragraph. Reconsideration and withdrawal of the rejection of Claims 31-44 under 35 U.S.C. §112, first paragraph, is therefore respectfully requested.

Rejections under 35 U.S.C. §102(a)

Claims 31-44 were rejected under 35 U.S.C. §102(a) as being clearly anticipated by Johnson et al. (PNAS 90:5677-5681, Jun. 1993). Additionally, Claims 31-33, 35-38, and 40-44 were rejected under 35 U.S.C. §102(a) as being clearly anticipated by Di Marco (J. Biol. Chem. 268:24290-24295, 15 Nov. 1993). In particular, the Examiner asserted that the Declaration filed on May 1, 2000 under 37 C.F.R. §1.131 is ineffective to overcome the Johnson et al. and DiMarco references because the Declaration fails to show that Applicants had established a practical utility for a receptor protein tyrosine kinase of the instant invention or an isolated nucleic acid encoding such a receptor prior to the publication of these references.

In response, Applicants submit that the Declaration clearly demonstrates conception and reduction to practice of the claimed subject matter prior to the effective filing date of Johnson (June, 1993) and DiMarco (Nov., 1993). Further, as discussed above, the present disclosure provides a specific, substantial, and credible utility for the claimed invention. Therefore, Applicants request full and favorable consideration of Declaration under 35 U.S.C. §1.131 filed on May 1, 2000.

In view of the above, Applicants submit that the isolated nucleic acid encoding a receptor claimed in Claims 31 and 36 had a specific, substantial, and credible utility before 1993 and that neither Johnson nor DiMarco are effective prior art references. Therefore, Applicants respectfully request that these rejections be reconsidered and withdrawn.

Rejection under 35 U.S.C. §102(b)

Claims 41-44 were rejected under 35 U.S.C. §102(b) as being anticipated by Klein et al. (EMBO J. 8(12):3701-3709, 1989). In particular, the Examiner asserted that "because any oligo

will bind to any nucleic acid under the appropriate conditions, these claims encompass any oligonucleotide." The Examiner also asserted that "since all nucleic acid molecules will bind (hybridize) to one another under certain conditions the oligonucleotide which was employed in Figure 1 of Klein et al. would certainly bind to the nucleic acid molecule of any of Claims 41-44 under the appropriate conditions.

Applicants respectfully traverse this rejection.

Initially, Applicants note that the Examiner is using the sequence of a mouse trkb (i.e., Figure 1) to obviate a human sequence as in the present invention. Additionally, Claim 41 claims an isolated nucleic acid that will hybridize under stringent conditions, such as those conditions described in the specification on page 19, lines 7-18. Although non-homologous nucleic acids will hybridize under non-stringent conditions, only homologous nucleic acids will hybridize under stringent conditions. As shown in the attached sequence alignments, SEQ ID NO: 7 has an 18.68% homology with mouse trkb and SEQ ID NO: 3 has a 43.98% homology with mouse trkb, and both sequence alignments have many gaps in which there is no homology at all. These factors indicate a very poor case for hybridization of mouse trkb with SEQ ID NO: 7 and SEQ ID NO: 3 under stringent conditions. Thus, there would be no appreciable binding of trkb to the nucleic acid of the present invention, which requires stringent conditions for hybridization. Accordingly, the mouse trkb sequence of Klein et al. is not sufficiently homologous to the nucleic acid sequences claimed in the present invention, and cannot support a rejection under §102.

Because a reference must contain each and every element of the claimed invention within the four corners of the document for the reference to be anticipatory, and because Klein et al. do not disclose an isolated nucleic acid sequence as set forth in any one of Claims 41-44, Applicants

submit that the present invention is not anticipated by, or obvious over, Klein et al. and respectfully request that the Examiner reconsider and withdraw this rejection.

CONCLUSION

In light of the above, Applicants believe that this application is now in condition for allowance and therefore request favorable consideration.

If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

Respectfully submitted,

PIPER MARBURY RUDNICK & WOLFE

2/4/02
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All Other Cases

In re Brana (CA FC) 34 USPQ2d 1436 (3/30/1995)

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No. 93-1393

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Headnotes

PATENTS

1. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Application for pharmaceutical invention did not fail to disclose specific disease against which claimed compounds are useful, and thereby fail to satisfy enablement requirement of 35 USC 112, since specification, which favorably compares compounds of invention with known compounds found to be highly effective against lymphocytic leukemia tumor models, implicitly asserts that claimed compounds are also highly effective against those models, and since tumor models are cell lines representing specific l ymphocytic tumors.

2. Patentability/Validity -- Utility (§ 115.10)

Patentability/Validity -- Specification -- Enablement (§ 115.1105)

Patent and Trademark Office improperly rejected, for lack of utility, application claims for pharmaceutical compounds used in cancer treatment in humans, since neither nature of invention nor evidence proferred by PTO would cause one of ordinary skill in art to reasonably doubt asserted utility, and since even if utility of compounds could be reasonably questioned, evidence that compounds within scope of claims, and other structurally similar compounds, are effective as chemotherapeutic agents in anim als would be sufficient to convince one skilled in art of asserted utility; absence of evidence that claimed compounds have chemotherapeutic effect in humans does not warrant contrary conclusion, since proof of alleged pharmaceutical property for compound by statistically significant tests using standard experimental animals is sufficient to establish utility.

Case History and Disposition:

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Appeal from the U.S. Patent and Trademark Office, Board of Patent Appeals and Interferences.

Patent application of Miguel F. Brana, Jose M.C. Berlanga, Marina M. Moset, Erich Schlick and Gerhard Keilhauer, serial no. 07/533,944, filed June 4, 1990, which is a continuation of serial no. 213,690, filed June 30, 1988. From decision upholding examiner's rejection of claims 10-13, applicants appeal. Reversed.

Attorneys:
Malcolm J. MacDonald, Herbert B. Keil, and David S. Nagy, Washington, D.C., for appellants.

Fred E. McKelvey, Solicitor, PTO; Albin F. Drost, Deputy Solicitor; Richard E. Schafer, Teddy S. Gron, Joseph G. Piccolo and Richard L. Torczon, Associate Solicitors, for appellee.

Judge:
Before Plager, Lourie, and Rader, circuit judges.

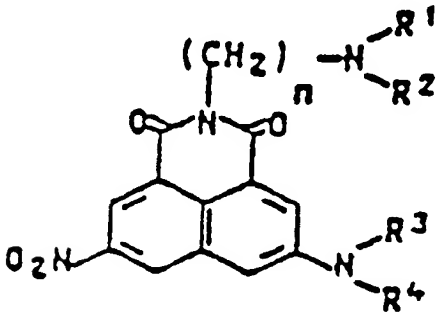
Opinion Text

Opinion By:
Plager, J.

Miguel F. Brana, *et al.* (applicants), appeal the March 19, 1993 decision of the United States Patent and Trademark Office (PTO) Board of Patent Appeals and Interferences (Board), in Appeal No. 92-1196. The Board affirmed the examiner's rejection of claims 10-13 of patent application Serial No. 533,944 under 35 U.S.C. Section 112 Para.1 (1988). 1 The examiner's rejection, upon which the Board relied in rendering its decision, was based specifically on a challenge to the utility of the claimed compounds and the amount of experimentation necessary to use the compounds. We conclude the Board erred, and reverse.

I. BACKGROUND

On June 30, 1988, applicants filed patent application Serial No. 213,690 (the '690 application) 2 directed to 5-nitrobenzo [de]isoquinoline-1,3-dione compounds, for use as antitumor substances, having the following formula:



where n is 1 or 2, R [1] and R [2] are identical or different and are each hydrogen,

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C1-C6-alkyl, C1-C6-hydroxyalkyl, pyrrolidinyl, morpholino, piperidinyl or piperacinyl, and R [3] and R [4] are identical or different and are each hydrogen, C1-C6-alkyl, C1-C6-acyl, C2-C7-alkoxycarbonyl, ureyl, aminocarbonyl or C2-C7-alkylaminocarbonyl. These claimed compounds differ from several prior art benzo [de]isoquinoline-1,3-dione compounds due to the presence of a nitro group (O2N) at the 5-position and an amino or other amino group (NR [3] R [4]) at the 8-position of the isoquinoline ring.

The specification states that these non- symmetrical substitutions at the 5- and 8-positions produce compounds with "a better action and a better action spectrum as antitumor substances" than known benzo [de]isoquinolines, namely those in K.D. Paull et al., *Computer Assisted Structure- Activity Correlations, Drug Research, 34(II),* 1243-46 (1984) (Paull). Paull describes a computer-assisted evaluation of benzo [de]isoquinoline-1,3-diones and related compounds which have been screened for antitumor activity by testing their efficacy *in vivo* 3 against two specific implanted murine (i.e., utilizing mice as test subjects) lymphocytic leukemias, P388 and L1210. 4 These two *in vivo* tests are widely used by the National Cancer Institute (NCI) to measure the antitumor properties of a compound. Paull noted that one compound in particular, benzo [de]isoquinoline-1,3(2H)dione,5-amino-2(2-dimethyl-aminoethyl [sic]) (hereinafter "NSC 308847"), was found to show excellent activity against these two specific tumor models. Based on their analysis, compound NSC 308847 was selected for further studies by NCI. In addition to comparing the effectiveness of the claimed compounds with structura lly similar compounds in Paull, applicants' patent specification illustrates the cytotoxicity of the claimed compounds against human tumor cells, *in vitro,* 5 and concludes that these tests "had a good action." 6

The examiner initially rejected applicants' claims in the '690 application as obvious under 35 U.S.C. Section 103 in light of U.S. Patent No. 4,614,820, issued to and referred to hereafter as Zee-Cheng *et al.* Zee-Cheng *et al.* discloses a benzo [de]isoquinoline compound for use as an antitumor agent with symmetrical substitutions on the 5-position and 8-position of the quinoline ring; in both positions the substitution was either an amino or nitro group. 7 Although not identical to the applicants' claimed compounds, the examiner noted the similar substitution pattern (i.e., at the same positions on the isoquinoline ring) and concluded that a mixed substitution of the invention therefore would have been obvious in view of Zee-Cheng *et al.*

In a response dated July 14, 1989, the applicants rebutted the Section 103 rejection. Applicants asserted that their mixed disubstituted compounds had unexpectedly better antitumor properties than the symmetrically substituted compounds in Zee-Cheng *et al.* In support of this assertion applicants attached the declaration of Dr. Gerhard Keilhauer. In his declaration Dr. Keilhauer reported that his tests indicated that applicants' claimed compounds were far more effective as antitumor agents than the compounds disclosed in Zee-Cheng *et al.* when tested, *in vitro,* against two specific types of human tumor cells, HEp and HCT-29. 8 Applicants further noted that, although the differences between the compounds in Zee-Cheng *et al.* and applicants' claimed compounds were slight, there was no suggestion in the art that these improved results (over Zee-Cheng *et al.*) would have been expected. Although the applicants overcame the Section 103 rejection, the examiner nevertheless issued a final rejection, on different grounds, on September 5, 1989.

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On June 4, 1990, applicants filed a continuation application, Serial No. 533,944 (the '944 application), from the above-mentioned '690 application. Claims 10-13, the only claims remaining in the continuation application, were rejected in a final office action dated May 1, 1991. Applicants appealed the examiner's final rejection to the Board.

In his answer to the applicants' appeal brief, the examiner stated that the final rejection was based on 35 U.S.C. Section 112 Para.1. 9 The examiner first noted that the specification failed to describe any specific disease against which the claimed compounds were active. Furthermore, the examiner concluded that the prior art tests performed in Paull and the tests disclosed in the specification were not sufficient to establish a reasonable expectation that the claimed compounds had a practical utility (i.e. antitumor activity in humans). 10

In a decision dated March 19, 1993, the Board affirmed the examiner's final rejection. The three-page opinion, which lacked any additional analysis, relied entirely on the examiner's reasoning. Although noting that it also would have been proper for the examiner to reject the claims under 35 U.S.C. Section 101, the Board affirmed solely on the basis of the Examiner's Section 112 Para.1 rejection. This appeal followed.

II. DISCUSSION

At issue in this case is an important question of the legal constraints on patent office examination practice and policy. The question is, with regard to pharmaceutical inventions, what must the applicant prove regarding the practical utility or usefulness of the invention for which patent protection is sought. This is not a new issue; it is one which we would have thought had been settled by case law years ago. 11 We note the Commissioner has recently addressed this question in his Examiner Guidelines for Biotech Applications, *see* 60 Fed. Reg. 97 (1995); 49 Pat. Trademark & Copyright J. (BNA) No. 1210, at 234 (Jan. 5, 1995).

The requirement that an invention have utility is found in 35 U.S.C. Section 101: "Whoever invents . . . any new and *useful* . . . composition of matter . . . may obtain a patent therefor. . . ." (emphasis added). It is also implicit in Section 112 Para.1, which reads:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Obviously, if a claimed invention does not have utility, the specification cannot enable one to use it.

As noted, although the examiner and the Board both mentioned Section 101, and the rejection appears to be based on the issue of whether the compounds had a practical utility, a Section 101 issue, the rejection according to the Board stands on the requirements of Section 112 Para.1. It is to that provision that we address ourselves. 12 The Board gives two reasons for the rejection; 13 we will consider these in turn.

1.

The first basis for the Board's decision was that the applicants' specification failed to disclose a specific disease against which the

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claimed compounds are useful, and therefore, absent undue experimentation, one of ordinary skill in the art was precluded from using the invention. *See Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F. 2d 1367, 1384, 231 USPQ 81 , 94 (Fed. Cir. 1986), *cert. denied,* 480 U.S. 947 (1987). In support, the Commissioner argues that the disclosed uses in the '944 application, namely the "treatment of diseases" and "antitumor substances," are similar to the nebulous disclosure found insufficient in *In re Kirk,* 376 F. 2d 936, 153 USPQ 48 (CCPA 1967). This argument is not without merit.

In *Kirk* applicants claimed a new class of steroid compounds. One of the alleged utilities disclosed in the specification was that these compounds possessed "high biological activity." *Id.* at 938, 153 USPQ at 50 . The specification, however, failed to disclose which biological properties made the compounds useful. Moreover, the court found that known specific uses of similar compounds did not cure this defect since there was no disclosure in the specification that the properties of the claimed compounds were the same as those of the known similar compounds. *Id.* at 942, 153 USPQ at 53 . Furthermore, it was not alleged that one of skill in the art would have known of any specific uses, and therefore, the court concluded this alleged use was too obscure to enable one of skill in the art to use the claimed invention. *See also Kawai v. Metlesics,* 480 F. 2d 880, 178 USPQ 158 (CCPA 1973).

[1] *Kirk* would potentially be dispositive of this case were the above-mentioned language the only assertion of utility found in the '944 application. Applicants' specification, however, also states that the claimed compounds have "a better action and a better action spectrum as antitumor substances" than known compounds, specifically those analyzed in Paull. As previously noted, *see supra* note 4, Paull grouped various benzo [de]isoquinoline-1,3-diones, which had previously been tested *in vivo* for antitumor activity against two lymphocytic leukemia tumor models (P388 and L1210), into various structural classifications and analyzed the test results of the groups (i.e. what percent of the compounds in the particular group showed success against the tumor models). Since one of the tested compounds, NSC 308847, was found to be highly effective against these two lymphocytic leukemia tumor models, 14 applicants' favorable comparison implicitly asserts that their claimed compounds are highly effective (i.e. useful) against lymphocytic leukemia. An alleged use against this particular type of cancer is much more specific than the vaguely intimated uses rejected by the

courts in *Kirk* and *Kawai. See, e.g., Cross v. Iizuka,* 753 F. 2d at 1048, 224 USPQ at 745 (finding the disclosed practical utility for the claimed compounds -- the inhibition of thromboxane synthetase in human or bovine platelet microsomes -- sufficiently specific to satisfy the threshold requirement in *Kirk* and *Kawai.*)

The Commissioner contends, however, that P388 and L1210 are not diseases since the only way an animal can get sick from P388 is by a direct injection of the cell line. The Commissioner therefore concludes that applicants' reference to Paull in their specification does not provide a specific disease against which the claimed compounds can be used. We disagree.

As applicants point out, the P388 and L1210 cell lines, though technically labeled tumor models, were originally derived from lymphocytic leukemias in mice. Therefore, the P388 and L1210 cell lines do represent actual specific lymphocytic tumors; these models will produce this particular disease once implanted in mice. If applicants were required to wait until an animal naturally developed this specific tumor before testing the effectiveness of a compound against the tumor *in vivo,* as would be implied from the Commissioner's argument, there would be no effective way to test compounds *in vivo* on a large scale.

We conclude that these tumor models represent a specific disease against which the claimed compounds are alleged to be effective. Accordingly, in light of the explicit reference to Paull, applicants' specification alleges a sufficiently specific use.

2.

The second basis for the Board's rejection was that, even if the specification did allege a specific use, applicants failed to prove that the claimed compounds are useful. Citing various references, 15 the Board found, and the Commissioner now argues, that the tests offered by the applicants to prove utility

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were inadequate to convince one of ordinary skill in the art that the claimed compounds are useful as antitumor agents. 16

This court's predecessor has stated:

[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of Section 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

In re Marzocchi, 439 F. 2d 220, 223, 169 USPQ 367 , 369 (CCPA 1971). From this it follows that the PTO has the initial burden of challenging a presumptively correct assertion of utility in the disclosure. *Id.* at 224, 169 USPQ at 370 . Only after the PTO provides evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility does the burden shift to the applicant to provide rebuttal evidence sufficient to convince such a person of the invention's asserted utility. *See In re Bundy,* 642 F. 2d 430, 433, 209 USPQ 48 , 51 (CCPA 1981). 17

[2] The PTO has not met this initial burden. The references cited by the Board, Pazdur and Martin, 18 do not question the usefulness of any compound as an antitumor agent or provide any other evidence to cause one of skill in the art to question the asserted utility of applicants' compounds. Rather, these references merely discuss the therapeutic predictive value of *in vivo* murine tests -- relevant only if applicants must prove the ultimate value in humans of their asserted utility. Likewise, we do not find that the nature of applicants' invention alone would cause one of skill in the art to reasonably doubt the asserted usefulness.

The purpose of treating cancer with chemical compounds does not suggest an inherently unbelievable undertaking or involve implausible scientific principles. *In re Jolles,* 628 F. 2d at 1327, 206 USPQ at 890 . Modern science has previously identified numerous successful chemotherapeutic agents. In addition, the prior art, specifically Zee Cheng *et al.* , discloses structurally similar compounds to those claimed by the applicants which have been proven *in vivo* to be effective as chemotherapeutic agents against various tumor models.

Taking these facts -- the nature of the invention and the PTO's proffered evidence -- into consideration we conclude that one skilled in the art would be without basis to reasonably doubt applicants' asserted utility on its face. The PTO thus has not satisfied its initial burden. Accordingly, applicants should not have been required to substantiate their presumptively correct disclosure to avoid a rejection under the first paragraph of Section 112. *See In re Marzocchi,* 439 F. 2d at 224, 169 USPQ at 370 .

We do not rest our decision there, however. Even if one skilled in the art would have reasonably questioned the asserted utility, i.e., even if the PTO met its initial burden thereby shifting the burden to the applicants to offer rebuttal evidence, applicants proffered sufficient evidence to convince one of skill in the art of the asserted utility. In particular, applicants provided through Dr. Kluge's declaration 19 test results showing that several compounds within the scope of the claims exhibited significant antitumor activity against the L1210 standard tumor

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model *in vivo.* Such evidence alone should have been sufficient to satisfy applicants' burden.

The prior art further supports the conclusion that one skilled in the art would be convinced of the applicants' asserted utility. As previously mentioned, prior art -- Zee Cheng *et al.* and Paull -- disclosed structurally similar compounds which were proven *in vivo* against various tumor models to be effective as chemotherapeutic agents. Although it is true that minor changes in chemical compounds can radically alter their effects on the human body, *Kawai,* 480 F. 2d at 891, 178 USPQ at 167 , evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility. *See Rey-Bellet v. Engelhardt,* 493 F. 2d 1380, 181 USPQ 453 (CCPA 1974); *Kawai,* 480 F. 2d 880, 178 USPQ 158 .

The Commissioner counters that such *in vivo* tests in animals are only preclinical tests to determine whether a compound is suitable for processing in the second stage of testing, by which he apparently means *in vivo* testing in humans, and therefore are not reasonably predictive of the success of the claimed compounds for treating cancer in humans. 20 The Commissioner, as did the Board, confuses the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption. *See Scott v. Finney,* 34 F. 3d 1058, 1063, 32 USPQ2d 1115 , 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and

Trademark Office (PTO) proceedings.").

Our court's predecessor has determined that proof of an alleged pharmaceutical property for a compound by statistically significant tests with standard experimental animals is sufficient to establish utility. *In re Krimmel,* 292 F. 2d 948, 953, 130 USPQ 215 , 219 (CCPA 1961); *see also In re Bergel,* 292 F. 2d 958, 130 USPQ 205 (CCPA 1961). In concluding that similar *in vivo* tests were adequate proof of utility the court in *In re Krimmel* stated:

We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.

Krimmel, 292 F. 2d at 953, 130 USPQ at 219 . Moreover, NCI apparently believes these tests are statistically significant because it has explicitly recognized both the P388 and L1210 murine tumor models as standard screening tests for determining whether new compounds may be useful as antitumor agents.

In the context of this case the Martin and Pazdur references, on which the Commissioner relies, do not convince us otherwise. Pazdur only questions the reliability of the screening tests against lung cancer; it says nothing regarding other types of tumors. Although the Martin reference does note that some laboratory oncologists are skeptical about the predictive value of *in vivo* murine tumor models for human therapy, Martin recognizes that these tumor models continue to contribute to an increasing human cure rate. In fact, the authors conclude that this perception (i.e. lack of predictive reliability) is not tenable in light of present information.

On the basis of animal studies, and controlled testing in a limited number of humans (referred to as Phase I testing), the Food and Drug Administration may authorize Phase II clinical studies. *See* 21 U.S.C. Section 355(i)(1); 5 C.F.R. Section 312.23 (a)(5), (a)(8) (1994). Authorization for a Phase II study means that the drug may be administered to a larger number of humans, but still under strictly supervised conditions. The purpose of the Phase II study is to determine primarily the safety of the drug when administered to a larger human population, as well as its potential efficacy under different dosage regimes. *See* 21 C.F.R. Section 312.21(b).

FDA approval, however, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott,* 34 F. 3d 1058, 1063, 32 USPQ2d 1115 , 1120 . Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the

associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer.

In view of all the foregoing, we conclude that applicants' disclosure complies with the requirements of 35 U.S.C. Section 112 Para.1.

3.

The Commissioner takes this opportunity to raise the question of this court's standard of review when deciding cases on appeal from the PTO. Traditionally we have recited our standard of review to be, with regard to questions of law, that review is without deference to the views of the Agency, *In re Donald son,* 16 F. 3d 1189, 1192, 29 USPQ2d 1845 , 1848 (Fed. Cir. 1994) (in banc), *In re Caveney,* 761 F. 2d 671, 674, 226 USPQ 1 , 3 (Fed. Cir. 1985), and with regard to questions of fact, we defer to the Agency unless its findings are "clearly erroneous." *See, e.g., In re Baxter Travenol Labs,* 952 F. 2d 388, 21 USPQ2d 1281 (Fed. Cir. 1991); *In re Woodruff,* 919 F. 2d 1575, 16 USPQ2d 1934 (Fed. Cir. 1990); *In re De Blauwe,* 736 F. 2d 699, 222 USPQ 191 (Fed. Cir. 1984).

With regard to judgment calls, those questions that fall " [s]omewhere near the middle of the fact-law spectrum," this court has recognized "the falseness of the fact-law dichotomy, since the determination at issue, involving as it does the application of a general legal standard to particular facts, is probably most realistically described as neither of fact nor law, but mixed." *Campbell v. Merit Systems Protection Board,* 27 F. 3d 1560, 1565 (Fed. Cir. 1994). When these questions of judgment are before us, whether we defer, and the extent to which we defer, turns on the nature of the case and the nature of the judgment. *Id.* ("Characterization therefore must follow from an *a priori* decision as to whether deferring . . . is sound judicial policy. We would be less than candid to suggest otherwise.").

The Commissioner contends that the appropriate standard of review for this court regarding questions of law, of fact, and mixed questions of law and fact, coming to us from the PTO is found in the Administrative Procedure Act (APA) at 5 U.S.C. Section 706. The standard set out there is that " [t]he reviewing court shall . . . hold unlawful and set aside agency action, findings, and conclusions found to be -- (A) arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law; . . . (E) unsupported by substantial evidence. . . ." The Commissioner is of the view that the stated standard we now use, which is the traditional standard of review for matters coming from a trial court, is not appropriate for decisions coming from an agency with presumed expertise in the subject area, and is not in accord with law. 21

Applicants argue that by custom and tradition, recognized by the law of this court, the standard of review we have applied, even though inconsistent with the standard set forth in the APA, nevertheless is a permissible standard. In our consideration of this issue, there is a reality check: would it matter to the outcome in a given case which formulation of the standard a court articulates in arriving at its decision? The answer no doubt must be that, even though in some cases it might not matter, in others it would, otherwise the lengthy debates about the meaning of these formulations and the circumstances in which they apply would be unnecessary.

A preliminary question, then, is whether this is one of those cases in which a difference in the standard of review would make a difference in the outcome. The ultimate issue is whether the Board correctly applied the Section 112 Para.1 enablement mandate and its implicit requirement of practical utility, or perhaps more accurately the underlying requirement of Section 101, to the facts of this case. As we have explained, the issue breaks down into two subsidiary issues: (1) whether a person of ordin ary skill in the art would conclude that the applicants had sufficiently described particular diseases addressed by the invention, and (2) whether the Patent Act supports a requirement that makes human testing a prerequisite to patentability under the circumstances of this case.

The first subsidiary issue, whether the application adequately described particular diseases, calls for a judgment about what the various representations and discussions contained in the patent application's specification would say to a person of ordinary skill in

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the art. We have considered that question carefully, and, for the reasons we explained above in some detail, we conclude that the Board's judgment on this question was erroneous. Our conclusion rests on our understanding of what a person skilled in the art would gather from the various art cited, and from the statements in the application itself. We consider the Board's error to be sufficiently clear that it is reversible whether viewed as clear error or as resulting in an arbitrary and capricious dec ision.

The second subsidiary issue, whether human testing is a prerequisite to patentability, is a pure question of law: what does the practical utility requirement mean in a case of this kind. Under either our traditional standard or under the APA standard no deference is owed the Agency on a question of law, and none was accorded.

If the question concerning the standard of review, raised by the Commissioner, is to be addressed meaningfully, it must arise in a case in which the decision will turn on that question, and, recognizing this, the parties fully brief the issue. This is not that case. We conclude that it is not necessary to the disposition of this case to address the question raised by the Commissioner; accordingly, we decline the invitation to do so.

III. CONCLUSION

The Board erred in affirming the examiner's rejection under 35 U.S.C. Section 112 Para.1. The decision is reversed. *REVERSED* .

Footnotes

Footnote 1. Unless otherwise noted, all United States Code citations are to the 1988 edition.

Footnote 2. This is a divisional of patent application Serial No. 110,871 filed October 21, 1987.

Footnote 3. *In vivo* means " [i]n the living body, referring to a process occurring therein." *Steadman's Medical Dictionary* 798 (25th ed. 1990). *In vitro* means " [i]n an artificial environment, referring to a process or reaction occurring therein, as in a test tube or culture media." *Id.*

Footnote 4. The analysis in Paull consisted of grouping the previously-tested compounds into groups based on common structural features and cross- referencing the various groups, in light of the success rates of the group as a whole, to determine specific compounds that may be effective in treating tumors.

Footnote 5. *See supra* note 3.

Footnote 6. The specification does not state the specific type of human tumor cells used in this test.

Footnote 7. The chemical compound in Zee-Cheng *et al.* is labeled a 3,6-disubstituted-1,8-naphthalimide and uses different numbering for the positions on the isoquinoline ring. The structure of this compound, however, is identical to that claimed by the applicants except for symmetrical substitutions at the 5-position and the 8-position of the isoquinoline ring. Zee-Cheng *et al.* teaches identical substitutions of amino or nitro groups while applicants claim a nitro group substitution at the 5-position and an amino group substitution at the 8-position.

Footnote 8. HEp cells are derived from laryngeal cancer and HCT-29 cells from colon cancer.

Footnote 9. The examiner's answer noted that the final rejection also could have been made under 35 U.S.C. Section 101 for failure to disclose a practical utility.

Footnote 10. The examiner subsequently filed two supplemental answers in response to arguments raised by the applicants in supplemental reply briefs.

Footnote 11. *See, e.g., Cross v. Iizuka,* 753 F. 2d 1040, 224 USPQ 739 (Fed. Cir. 1985); *In re Langer,* 503 F. 2d 1380, 183 USPQ 288 (CCPA 1974); *In re Krimmel,* 292 F. 2d 948, 130 USPQ 215 (CCPA 1961); *In re Bergel,* 292 F. 2d 958, 130 USPQ 205 (CCPA 1961).

Footnote 12. This court's predecessor has determined that absence of utility can be the basis of a rejection under both 35 U.S.C. Section 101 and Section 112 Para.1. *In re Jolles,* 628 F. 2d 1322, 1326 n.11, 206 USPQ 885 , 889 n.11 (CCPA 1980); *In re Fouche,* 439 F. 2d 1237, 1243, 169 USPQ 429 , 434 (CCPA 1971) (" [I]f such compositions are in fact useless, appellant's specification cannot have taught how to use them."). Since the Board affirmed the examiner's rejection based solely on Section 112 Para.1, however, our review is limited only to whether the application complies with Section 112 Para.1.

Footnote 13. The Board's decision did not expressly make any independent factual determinations or legal conclusions. Rather, the Board stated that it "agree [d] with the examiner's well reasoned, well stated and fully supported by citation of relevant precedent position in every particular, and any further comment which we might add would be redundant." *Ex parte Brana et al.* , No. 92-1196 (Bd. Pat. App. & Int. March 19, 1993) at 2-3. Therefore, reference in this opinion to Board findings are actually arguments made by the examiner which have been expressly adopted by the Board.

Footnote 14. Paull also found NSC 308847 to be effective against two other test models, B16 melanoma and Colon C872.

Footnote 15. *See* Pazdur et al., *Correlation of Murine Antitumor Models in Predicting Clinical Drug Activity in Non-Small Cell Lung Cancer: A Six Year Experience,* 3 *Proceedings Am. Soc. Clin. Oncology* 219 (1984); Martin et al., *Role of Murine Tumor Models in Cancer Research,* 46 *Cancer Research* 2189 (April 1986).

Footnote 16. As noted, this would appear to be a Section 101 issue, rather than Section 112.

Footnote 17. *See also In re Novak,* 306 F. 2d 924, 928, 134 USPQ 335 , 337 (CCPA 1962) (stating that it is proper for the examiner to request evidence to substantiate an asserted utility unless one with ordinary skill in the art would accept the allegations as obviously valid and correct); *In re Chilowsky,* 229 F. 2d 457, 462, 108 USPQ 321 , 325 (CCPA 1956) (" [W]here the mode of operation alleged can be readily understood and conforms to the known laws of physics and chemistry . . . no further evidence is required."). *But see In re Marzocchi,* 439 F. 2d at 223, 169 USPQ at 369-70 ("In the field of chemistry generally there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the

accuracy of a particular broad statement put forward as enabling support for a claim. This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles.").

Footnote 18. *See supra* note 15.

Footnote 19. The declaration of Michael Kluge was signed and dated June 19, 1991. This declaration listed test results (i.e. antitumor activity) of the claimed compounds, *in vivo,* against L1210 tumor cells and concluded that these compounds would likely be clinically useful as anti-cancer agents. Enablement, or utility, is determined as of the application filing date. *In re Glass,* 492 F. 2d 1228, 1232, 181 USPQ 31 , 34 (CCPA 1974). The Kluge declaration, though dated after applicants' filing date, can be used to substantiate any doubts as to the asserted utility since this pertains to the accuracy of a statement already in the specification. *In re Marzocchi,* 439 F. 2d at 224 n.4, 169 USPQ at 370 n.4. It does not render an insufficient disclosure enabling, but instead goes to prove that the disclosure was in fact enabling when filed (i.e., demonstrated utility).

Footnote 20. We note that this discussion is relevant to the earlier discussion as well. If we were to conclude that these *in vivo* tests are insufficient to establish usefulness for the claimed compounds, that would bear on the issue of whether one skilled in the art would, in light of the structurally similar compounds in Paull and Zee Cheng *et al.* , have cause to doubt applicants' asserted usefulness for the compounds.

Footnote 21. Congress enacted the Administrative Procedure Act (APA) on June 11, 1946. *See* 1 *Kenneth Culp Davis, Administrative Law Treatise,* Section 1:7 (2d ed. 1978). The APA sets forth a framework for administrative agency procedure and provides judicial review for persons adversely affected by final agency actions. Chapter 7, codified at 5 U.S.C. Sections 701-706, contains the APA judicial review provisions, including the standard of review provision quoted above.

- End of Case -

In re Kirk and Petrow, 153 USPQ 48 (CCPA 1967)

In re Kirk and Petrow

(CCPA)
153 USPQ 48

Decided Mar. 16, 1967
Appl. No. 7522
U.S. Court of Customs and Patent Appeals

Headnotes

PATENTS

1. Specification - Sufficiency of disclosure (§ 62.7)

Specification does not comply with 35 U.S.C. 101 and 112 since nebulous expressions "biological activity" and "biological properties" do not contain a sufficiently explicit indication of usefulness of compounds and how to use them.

2. Specification - Sufficiency of disclosure (§ 62.7)

Congress intended 35 U.S.C. 112 to presuppose full satisfaction of requirements of section 101; necessarily, compliance with section 112 requires a description of how to use presently useful inventions; disclosure is insufficient where experimentation is necessary to determine actual uses, or possible lack of uses, of compounds, as well as how to employ them in a useful manner.

3. Patentability - Utility (§ 51.75)

Specification - Sufficiency of disclosure (§ 62.7)

It cannot be presumed that a steroid chemical compound is "useful" under 35 U.S.C. 101, or that one skilled in the art will know "how to use" it, simply because compound is closely related only in a structural sense to other steroid compounds known to be useful.

4. Patentability - Utility (§ 51.75)

Specification - Sufficiency of disclosure (§ 62.7)

Just as practical utility of compound produced by chemical process is essential element in establishing patentability of process, so the practical utility of compound produced by chemical intermediate, the starting material in such a process, is essential element in establishing patentability of intermediate; if process for producing product of only conjectural use is not itself useful within 35 U.S.C. 101, it cannot be said that starting materials for such a process, i.e., intermediates, are useful; it is not enough that specification disclose that intermediate exists and that it reacts, or can be used to produce intended product of no known use, nor is it enough that product disclosed to be obtained from intermediate belongs to some class of compounds which now is, or in the future might be, subject of research to determine some specific use; to extent that In re Nelson, 126 USPQ 242 , In re Wilke, 136 USPQ 435 , In re Adams, 137 USPQ 333 , and In re Szwarc, 138 USPQ 208 , are inconsistent with the above or with Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 , they are overruled.

Particular patents-Steroid Compounds

Kirk and Petrow, 1-Dehydro-6-Methyl Steroid Compounds, claims 11, 25, 26, 28, 29, 39, 41, and 45 of application refused.

Case History and Disposition:

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Appeal from Board of Appeals of the Patent Office.

Application for patent of David Neville Kirk and Vladimir Petrow, Serial No. 796,749, filed Mar. 3, 1959; Patent Office Group 120. From decision rejecting claims 11, 25, 26, 28, 29, 39, 41, and 45, applicants appeal. Affirmed; Rich and Smith, Judges, dissenting with opinions; Worley, Chief Judge, specially concurring with opinion.

See also 153 USPQ 266 .

Attorneys:

Bacon & Thomas (Jesse B. Grove, Jr., of counsel) both of Washington, D. C., for appellants.

Clarence W. Moore (Jack E. Armore of counsel) for Commissioner of Patents.

Judge:

Before Worley, Chief Judge, Rich, Smith, and Almond, Associate Judges, and Kirkpatrick, Judge.

Opinion Text

Opinion By:

Worley, Chief Judge.

This appeal is from the decision of the Board of Appeals affirming the rejection of claims 11, 25, 26, 28, 29, 39, 41 and 45 in appellants' application [1] entitled "1-Dehydro-6-Methyl Steroid Compounds."

Each claim defines a specific steroid compound, claim 11 relating to a compound of the spirostane series; claims 25, 26, 28, 29 and 45 to compounds of the androstane series; and claims 39 and 41 to compounds of the pregnane series. It is unnecessary to reproduce any claim since the nature of the compounds will become apparent.

The Patent Office rejected all claims for failure of the specification "to comply with 35 U.S.C. 101 and 112." As we view the record, we are concerned with not only the legal adequacy of appellants' disclosure of "how to use" the claimed compounds under 35 U.S.C. 112, [2] but also the legal adequacy of assertions of usefulness in the original specification under 35 U.S.C. 101. [3] We

are particularly concerned with the applicability of the decision of the Supreme Court in Brenner v. Manson, 383 U.S. 519, 148 USPQ 689 , to the facts here. [4]

The appropriate starting point for disposition of those issues is appellants' specification, which begins with several general statements as to how the claimed compounds are useful:

> It is an object of the present invention to provide a process for the conversion of 3-oxo- D D 4 -6-methyl and 3-oxo- D D 4:6 - 6-methyl steroidal derivatives into the corresponding 1-dehydro-derivatives which are a new class of compounds *often possessing high biological activity.*
>
> The present invention provides new 1-dehydro-derivatives of 3-oxo- D D 4:6 - 6-methyl and certain 3-oxo- D D 4 -6-methyl steroids having the formula
> *Tabular, graphic, or textual material set at this point is not available. Please consult hard copy or call BNA PLUS at 1-800-452-7773 or 202-452-4323.*
>
> (with or without a double bond at the 6:7 position) which 1-dehydro-derivatives are of value *on account of their biological properties* or *as intermediates in the preparation of compounds with useful biological properties* as herein indicated or as is apparent to those skilled in the art.
>
> The invention also provides the following new steroidal 6-methyl-1:4-dien-3-ones and 6-methyl-1:4:6-trien-3-ones which are of value *in steroid technology, in the furtherance of steroidal research and in the application of steroidal materials* to veterinary or medical practice, whether as tablets, elixirs, injections, implants, or other types of pharmaceutical preparation well known to those skilled in the art. (Emphasis supplied)

The description continues with lists of specific compounds of the cholestane, spirostane, androstane and pregnane steroid series together with a recital of "uses" for the compounds recited in the lists. Two compounds of the spirostane series are disclosed, one of which, 6-hydroxy-6-methyl-25D-spirosta - 1:4-dien-3-one, is the subject of claim 11. They are said to be

> * * * of value as *intermediates in the preparation of 6-methylated aromatic steroid hormones* into which intermediates they may be converted by reaction in solution in acetic anhydride with toluene- *p* -sulphonic acid. (Emphasis supplied)

Eighteen compounds of the androstane series are disclosed. The five recited in the claims are

17 b -Hydroxy-6:17 a - dimethyland-rosta-1:4:6-trien-3-one [Claim 45]

17 a - Ethynyl-17 b -hydroxy-6-methylandrosta-1:4:6-trien-3-one [Claim 25]

17 b -Acetoxy-4:6 a -dimethylandrosta-1:4-dien-3-one [Claim 26]

9 a -Fluoro-11 b :17 b - dihydroxy-6 a :17 a -dimethylandrosta-1:4 - dien-3-one [Claim 28]

17 b -Hydroxy - 6 a -methyl-17 a -(prop-l-ynyl) androsta - 1:4-dien-3-one [Claim 29]

They are said to be

> * * * of value *as intermediates in the preparation of 6-methylated aromatic steroidal hormones,* into which they may be converted by reaction in solution in acetic anhydride with toluene- r -sulphonic acid, *as intermediates in the preparation of biologically active compounds and in some cases on account of their biological properties.* (Emphasis supplied)

Some sixteen compounds of the pregnane series are disclosed, including the two compounds of claims 39 and 41,

> 6 a -Methyl-16 a :17 a - *iso* propylidenedioxy - pregna - 1:4 - diene-3:20-dione [Claim 39] and
>
> 20:20 - Bisethylenedioxy - 6 a -methyl-pregna-1:4 - dien-3-one [Claim 41].

They are alleged to be

> * * * of value *as intermediates in the preparation of compounds with valuable biological properties such as progestational properties or properties associated with the adrenocortical hormones or as intermediates in the preparation of compounds with useful biological properties.* (Emphasis supplied)

Appellants' arguments are, in the main, two-fold. They first contend that

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the specification is adequate to comply with § 101 and § 112 because it discloses that the claimed compounds "have present and useful biological activity of the nature known for analogous steroidal compounds," and that "one skilled in the art would know how to use the compounds of the claims to take advantage of their presently-existing biological activity." The second argument is that the specification adequately discloses that the compounds "have use as intermediates in the production of aromatic steroid al hormones and other biologically useful compounds," and that the examiner has admitted one skilled in the art would know how to use the claimed compounds as intermediates for that purpose. The respective arguments present somewhat different considerations, and will be discussed separately.

I. The Asserted "Therapeutic" or "Biological" Activity

In his final rejection, the examiner stated:

> All the claims are again rejected as lacking adequate utility. The disclosure fails to indicate to one skilled in the art how one is to use the novel compounds of this invention. The therapeutic properties are stated in such general terms i.e., "useful biological properties", that it fails to convey any useful information to one skilled in the art and further fails to state which of the claimed compounds have a therapeutic activity. * * *

In response, appellants submitted argument that the rejection "is not warranted," and also submitted an affidavit of one of the applicants, a Dr. Petrow, which appellants summarized in a letter accompanying the affidavit and substantially reiterate in their brief here:

> Attached hereto is an affirmation of Vladimir Petrow which shows that one skilled in the art would be able to determine the biological uses of the claimed compounds by routine tests. The Petrow affirmation specifically shows that * * * [the steroid of] (Claim 25) in the well-known McPhail modification of the Clauberg Assay possesses progestational activity on oral administration. The natural hormone, progesterone, on the other hand shows no response on oral administration in the same test. Accordingly, i t is quite evident that the compound of claim 25 is a valuable oral progestational agent. This affirmation, accordingly, is proof of the fact that one skilled in the art would have no difficulty in determining whether *or not* the 1-dehydro derivatives of the pregnane series, as claimed, have value biologically as progestational agents. (Emphasis supplied)
>
> In addition, the Petrow affirmation * * * discloses the determination of the anabolic activity of * * * the compound of claim 26. It is shown by standard test procedure that this compound does have anabolic activity and that, in addition, it has a much higher anabolic/androgenic ratio than that of testosterone propionate, a well-known anabolic agent. * * *
>
> Further * * * the oral progestational activity of * * * the compound of claim 39, is set forth by virtue of *well-known test procedure*. This pregnane derivative is shown to be approximately 4 times as active progestationally on oral administration as * * * a well-known oral progestational agent. * * * by means of other tests the compound of claim 39 has been found to have valuable anti-inflammatory activity greater than that of either cortisone acetate or hydrocortisone. By virtue of a further standard test procedure the gluco corticoid activity of the compound of claim 39 has been shown to be more than 10 times that of cortisone and hydr ocortisone acetates.
>
> The affirmation of Dr. Petrow not only shows that the compounds claimed do have biological activity as asserted in the specification, but that the nature of such biological activity can be readily determined by those skilled in the art by reason of standard test procedures. [5]

Appellants' affidavit and argument went for naught, the examiner responding that

> * * * the final rejection of all the claims in the case as lacking an adequate disclosure of utility is deemed sound and adhered to. * * *
>
> In his Answer before the board, the examiner rejected the claims.
>
> * * * as failing to comply with 35 U.S.C. 101 and 112 in that the specification fails to teach those skilled in the art how to use the invention. * * *

After reviewing the various passages

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of appellants' specification relating to the uses of the claimed compounds and "how to use" them, he concluded:

> * * * nowhere is there found a *specific* allegation of utility for any compound within the scope of the claims. Thus the specification does not describe the manner in such full, clear, concise and exact terms as to enable one skilled in the steroid art to use the compounds of the instant invention. * * * Appellants have not listed one specific use for their claimed steroids and as those skilled in the art know steroids are susceptible to hundreds of uses. *What appellants are really saying to those in the art is take these steroids, experiment, and find what use they do have as medicines.* (Emphasis supplied)

With regard to the Petrow affidavit, the examiner stated:

> * * * it may be that oral progestational activity can be determined by procedures well known in the art. * * * Once one knows that a compound does have utility as a progestational agent, it is of course merely routine to determine at what doses this activity exists. In other words, if in the specification as filed there had been a specific allegation that the compounds herein claimed had progestational activity this would have been sufficient to satisfy 35 U.S.C. 112,- since those skilled in the art would know how to use a steroid possessing progestational activity. Thus, the aforementioned affidavit is not determinative of the issue at bar which is if the specification as filed does not allege a specific utility would one skilled in the art know how to use the invention?

The board agreed, adding that the reference in the specification to "biological properties" of the claimed compounds "is so general and vague as to be meaningless." It found in the specification no reason to expect that any of the claimed compounds "presents the probability of usefulness in the same manner as a natural hormone."

Appellants rely on the allegations in their specification that the disclosed compounds have "biological activity" as adequate disclosure of a use for the claimed compounds, stating:

> The disclosure teaches that the novel compounds are, in some cases, of value because of their presently existing biological activity. The application * * * teaches that such *steroidal* materials may be applied to veterinary or medical practice in the form of tablets, elixirs, injections, implants or other pharmaceutical preparations. In other words, the compounds in question are to be used *in the manner of other steroid hormones* in veterinary or medical compositions.

They also rely on the Petrow affidavit as evidence of the proposition that one skilled in the art would know how to use the claimed compounds, and assert that "the Board erroneously, completely ignored the Petrow affirmation confirming present useful hormonal activity of some of the compounds * * *."

[1] We are not persuaded by appellants' arguments that their specification meets the requirements of §§ 101 and 112. It seems to us that the nebulous expressions "biological activity" or "biological properties" appearing in the specification convey no more explicit indication of the usefulness of the compounds and how to use them than did the equally obscure expression "useful for technical and pharmaceutical purposes" unsuccessfully relied upon by the appellant in In re Diedrich, 50 CCPA 1355, 318 F. 2d 946, 138 USPQ 128 . [6]

Nor does the Petrow affidavit help appellants' cause here. While that affidavit may show that three of appellants' claimed compounds do *in fact* possess specific anabolic, anti-inflammatory or glucocorticoid activity or usefulness as oral progestational agents, that is not the issue before us. It is what the compounds are *disclosed* to do that is determinative here. In that regard, it is appropriate to note that the specification does not even intimate that the claimed compounds of the spirostane and pregnane series *themselves* have "biological activity," much less the specific progestational, glucocorticoid or anti-inflammatory activities mentioned in the affidavit. With respect to the eighteen androstanes that are disclosed, five of which are claimed here, it is said they "are of value * * * *in some cases* on account of their biological properties." (Emphasis supplied.) There is no suggestion *which* androstanes are of value for that reason, or *what* biological properties make them useful. [7]

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[2] Thus we agree with the solicitor that appellant's affidavit is simply an ex post facto affirmation irrelevant to the issue of adequacy of the original disclosure inasmuch as it attempts to add statements of usefulness to the disclosure of the application as filed. Indeed, the sum and substance of the affidavit appears to be that one of ordinary skill in the art would know "how to use" the compounds to find out in the first instance whether the compounds *are - or are not - in fact* useful or possess useful properties, and to ascertain what those properties are. It amounts to an admission that experimentation would be necessary to determine actual uses-or possible lack of uses-of the compounds, as well as how to employ them in a useful manner. But surely Congress intended § 112 to pre-suppose *full satisfaction* of the requirements of § 101. Necessarily, compliance with § 112 requires a description of how to use presently useful inventions, otherwise an applicant would anomalously be required to teach how to use a useless invention. As this court stated in Diedrich, quoting with approval from the decision of the board, 138 USPQ at 130 :

> We do not believe that it was the intention of the statutes to require the Patent Office, the courts, or the public to play the sort of guessing game that might be involved if an applicant could satisfy the requirements of the statutes by indicating the usefulness of a claimed compound in terms of possible use so general as to be meaningless and then, after his research or that of his competitors has definitely ascertained an actual use for the compound, adducing evidence intended to show that a particular specific use would have been obvious to men skilled in the particular art to which this use relates.

As the Supreme Court said in Brenner v. Manson, 148 USPQ at 696 :

> * * * a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion. * * *

Appellants further argue that the board had no grounds for concluding there was "no definite expectation from the specification" that any one of the claimed compounds "presents the probability of usefulness in the same manner as a natural hormone." According to appellants, "The analogy to known natural and synthetic hormones [presumably appellants intend to draw an analogy in chemical make-up or constitution between the claimed compounds and, for example, the natural hormone progesterone] enables one to pr edict that the new compounds would possess similar hormonal activity." Moreover, since some of the disclosed compounds of the pregnane series, not claimed here, were stated in the specification to be of value on account of their hydrocortisone-like anti-inflammatory properties, appellants contend that "it would not be unreasonable to predict that others of this series [i.e. the claimed pregnane derivatives] would also have this property."

[3] Similar arguments were advanced before, and rejected by, the Supreme Court in Brenner v. Manson, 383 U.S. at 531-2, 148 USPQ at 694 . We find no error in the board's position on the facts of this case, absent a disclosure in the specification that the requisite properties of the *claimed* compounds are also similar to those of a natural or synthetic hormone of known activity. Appellants' arguments fail to recognize that many steroid compounds may possess no activity whatsoever. It cannot be presumed that a *steroid* chemical compound is "useful" under § 101, or that one of skill in the art will know "how to use" it, simply because the compound is closely related only in a structural sense to other steroid compounds known to be useful. Cf. In re Adams, 50 CCPA 1185, 316 F. 2d 476, 137 USPQ 333 , dissenting opinion.

We conclude that appellants' specification does not comply with § 101 and § 112 merely on the statements of "biological" activity recited therein.

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II. The Asserted Usefulness as an "Intermediate"

As can be seen from the portions of the specification quoted earlier, appellants disclose that the claimed spirostane and androstane derivatives may be used as intermediates in the formation of 6-methyl aromatic steroids, and that the claimed pregnane derivatives may similarly be employed to produce steroids having "progestational properties" or "properties associated with the adreno-cortical hormones." [8]

The examiner has conceded that "those skilled in the art would know how to produce aromatic steroids" from the claimed compounds. However, he did not believe the inquiry into the adequacy of the disclosure should stop there, noting:

> * * * As to the portions of the disclosure which indicates that the claimed compounds are useful as intermediates in the production of 6-methylated aromatic steroids, *applicants have failed to show even one useful aromatic steroid which corresponds to the claimed intermediates. In other words, applicants' statement of utility is to the effect that the novel compounds claimed herein are useful in making other novel compounds which have no known use.* In the examiner's opinion this is not sufficient nor does the Examiner know of any decision holding that such a statement is adequate. (Emphasis supplied)

Appellants contend that the examiner's holding [9]"is straight into the teeth" of the decision of this court in In re Nelson, 47 CCPA 1031, 280 F. 2d 172, 126 USPQ 242 . They urge that the present disclosure with respect to the usefulness of the claimed compounds as intermediates "is on all fours" with that in Nelson. In their view, the examiner's requirement for disclosure of a use of the final products produced by carrying out the known process on the novel intermediates of the claims "is an absurdity" in view of Nelson and the further decisions of this court in In re Wilke, 50 CCPA 964, 314 F. 2d 558, 136 USPQ 435 ; In re Adams; and In re Manson, 52 CCPA 739, 333 F. 2d 234, 142 USPQ 35 . They look upon the latter decisions as carrying forward the principle expressed in Nelson that, in their words, "there is no necessity for a specification to teach the use of an end product where such end product is not the invention claimed, but merely the result thereof."

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The decision in Nelson might well control here- *if* that decision were still a viable precedent. The question remains, however, whether the majority view in Nelson-that steroid chemical compounds may be useful under § 101 if they are useful to chemists doing research on steroids and can be used to produce steroids which are members of a general class some members of which are known to have useful therapeutic properties-can possibly remain the law in view of Brenner v. Manson.

There the Supreme Court, in considering what renders a process useful under § 101, discussed the cases cited by appellants here, stating (all emphasis supplied), 148 USPQ at 693-694 :

> As is so often the case, however, a simple, everyday word [useful] can be pregnant with ambiguity when applied to the facts of life. That this is so is demonstrated by the *present conflict between the Patent Office and the CCPA* over how the test is to be applied to a chemical process which yields an already known product whose utility- *other than as a possible object of scientific inquiry* -has not yet been evidenced. It was not long ago that agency and court seemed of one mind on the question. In Application of Bremner, 37 CCPA 1032, 1034, 182 F. 2d 216, 217, 86 USPQ 74 , 75 , the court affimed rejection by the Patent Office of both process and product claims. It noted that "no use for the products claimed to be developed by the processes had been shown in the specification." It held that "It was never intended that a patent be granted upon a product, or a process producing a product, unless such product be useful." Nor was this new doctrine in the court. See Thomas v. Michael, 35 CCPA 1036, 1038-1039, 166 F. 2d 944, 946-947, 77 USPQ 216 , 217-218 .
>
> The Patent Office has remained steadfast in this view. The CCPA, however, has moved sharply away from Bremner. The trend began in Application of Nelson, 47 CCPA 1031, 280 F. 2d 172, 126 USPQ 242 . There, the court reversed the Patent Office's rejection of a claim on a process [product] yielding chemical intermediates "useful to chemists doing research on steroids," *despite the absence of evidence that any of the steroids thus ultimately produced were themselves "useful."* The *trend has accelerated,* [10]*culminating in* the present case where the court held it sufficient that a process produces the result intended and is not "detrimental to the public interest." 52 CCPA at 745, 333 F. 2d at 238, 142 USPQ at 38 .

Stripped of the highly technical procedural differences, the basic issue here, as in Brenner v. Manson, is whether the burden resting on an applicant to show that his invention is useful within the requirements of § 101 has been satisfied. While Manson did not disclose any use at all for the steroid compounds produced by his process, the arguments he advanced as to why those compounds were useful under § 101 correspond in substantial measure to the disclosure of the specification and the arguments relied o n here. There can be no doubt that the insubstantial, superficial nature of vague, general disclosures or arguments of "useful in research" or "useful as building blocks of value to the researcher" was recognized, and clearly rejected, by the Supreme Court, 148 USPQ at 695-696 :

> Whatever weight is attached to the value of encouraging disclosure and of inhibiting secrecy, *we believe a more compelling consideration is that a process patent in the chemical field, which has not been developed and pointed to the degree of specific utility,* creates a monopoly of knowledge which should be granted *only* if clearly commanded by the statute. * * * The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility. Unless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field.
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> *These arguments* for and against the patentability of a *process* which
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> Page 56
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> either *has no known use* or is *useful only in the sense that it may be an object of scientific research* would *apply equally* to the patenting of the *product produced by the process.* Respondent appears to concede that with respect to a product, as opposed to a process, Congress has struck the balance on the side of nonpatentability unless "utility" is shown. Indeed, the decisions of the CCPA are in accord with the view that a product may not be patented absent a showing of utility greater than any adduced in the present case. *We find absolutely no warrant for the proposition that although Congress intended that no patent be granted on a chemical compound whose sole "utility" consists of its potential role as an object of use-testing,* a different set of rules was meant to apply to the process which yielded the unpatentable product. *That proposition seems to us little more than an attempt to evade the impact of the rules which concededly govern patentability of the product itself.* (Emphasis supplied)

[4] Wholly aside from the controlling impact of that reasoning here, the conclusion is inescapable that, just as the practical utility of the compound produced by a chemical process "is an essential element" in establishing patentability of the process, 383 U.S. 519, 148 USPQ 689 , so the practical utility of the compound, or compounds, produced from a chemical "intermediate," the "starting material" in such a process, is an essential element in establishing patentability of that intermediate. It seems clear that, if a process for producing a product of only conjectural use is not itself "useful" within § 101, it cannot be said that the starting materials for such a process-i.e., the presently claimed intermediates - are "useful." It is not enough that the specification disclose t hat the intermediate exists and that it "works," reacts, or can be used to produce some intended product of no known use. Nor is it enough that the product disclosed to be obtained from the intermediate belongs to some class of compounds which now is, or in the future might be, the subject of research to determine some specific use. [11]Cf. Reiners v. Mehltretter, 43 CCPA 1019, 1026, 236 F. 2d 418, 421, 111 USPQ 97 , 100 , where compounds employed as intermediates to produce other *directly* useful compounds were found to be themselves useful.

It is impossible to reconcile the reasoning and conclusion of the majority in Nelson, Wilke, Adams and Szwarc with the majority view in Brenner v. Manson. Therefore, to the extent that those decisions are inconsistent with Brenner v. Manson and the views expressed herein, they must be, and are, overruled.

The decision is *affirmed.*

Footnotes

Footnote 1. Serial No. 796,749, filed March 3, 1959.

Footnote 2. 35 U.S.C. 112 reads in pertinent part:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Footnote 3. 35 U.S.C. 101 reads in pertinent part:

> Whoever invents or discovers any new and *useful* process, machine, manufacture, or *composition of matter,* or any new and useful improvement thereof, may obtain a patent therefor, *subject to the conditions and requirements of this title.* (Emphasis supplied)

Footnote 4. This appeal was originally argued December 7, 1965, some three months prior to the decision in Brenner v. Manson on March 21, 1966. On November 10, 1966, this court restored the appeal to the calendar for reargument, and requested counsel to file memoranda "on the effect, if any, of Brenner v. Manson * * * on this appeal." Argument on that question was heard December 5, 1966.

Footnote 5. The record shows that the "standard test procedures" involved the use of laboratory animals, specifically rats and rabbits.

Footnote 6. There this court affirmed the rejection of certain claims for failure of an application to comply with section 112, noting that it had no " *specific* disclosure as to just *how* the compounds are to be *used.* "

Footnote 7. Appellants also rely on this court's decisions in In re Hitchings, 52 CCPA 1141, 342 F. 2d 80, 144 USPQ 637 ; In re Dodson, 48 CCPA 1125, 292 F. 2d 943, 130 USPQ 224 ; In re Krimmel, 48 CCPA 1116, 292 F. 2d 948, 130 USPQ 215 ; and In re Bergel, 48 CCPA 1102, 292 F. 2d 955, 130 USPQ 206 , for the proposition that usefulness of compositions of matter under § 101 may be established by an appropriate demonstration that the composition has useful properties or activities when tested in laboratory animals. Appellants correctly point out that the Supreme Court in Brenner v. Manson neither approved nor disapproved the reasoning and conclusions of those cases, 383 U.S. 531, 148 USPQ 694 . However, appellants' reliance on those cases here appears misplaced. In those cases, the inventors had carried their invention substantially further than appellants here, pharmacological testing having proceeded to an extent that some particular salutary effects on conditions inimical to animals could be ascribed to the compounds in issue there. The general results of those tests were disclosed in the application as filed, in contrast to the situation here. See also Archer v. Papa, 46 CCPA 835, 265 F. 2d 954, 121 USPQ 413 ; Blicke v. Treves, 44 CCPA 753, 241 F. 2d 718, 112 USPQ 472 .

Footnote 8. The disclosure with respect to the claimed pregnanes was characterized by the board as "even less helpful as to the manner in which these compounds may be used." We note, as did the solicitor, that appellants do not *disclose* either broadly or specifically what steroids having "progestational" or "adreno-cortical" properties may be produced from the claimed pregnanes. There is no hint in the disclosure as to what additional molecular substituents, if any, must be present in the steroids to be produced from the claimed pregnanes to obtain the recited properties. Nor do appellants direct our attention to *any* specific compound, possessing some specific property and known to the art at the time they filed their application, which can be prepared from the claimed pregnanes.

Footnote 9. It is interesting to compare the rejections voiced by the examiner and board and summarized by the solicitor in Nelson, 47 CCPA 1037-9, 280 F. 2d 176-7, 126 USPQ 247 , with those raised here. For all intents and purposes, the rejections are identical. Although the board here found no decision "more directly relevant" than Nelson, nevertheless the examiner, board and solicitor all seek to distinguish it, urging that this court "evidently felt" that at least some of the products which could be made using Nelson's compounds as intermediates would be final products usable with no experimentation for specific therapeutic end purposes. The court did not intend Nelson to hav e the narrow scope attributed to it by the Patent Office. The most the court knew about what could be done with Nelson's C-19 14-hydroxy androstenes was that they could be used as intermediates to produce "steroids of a class at least some members of which are known to have useful therapeutic properties." The court took that as no guarantee that any of the *particular* "final products" which might be produced from Nelson's *particular* intermediates themselves would have the cardiac glycoside activity of other members of the class. As appellants correctly note in their brief:

> In the Nelson case, one skilled in the art could not exactly predict what therapeutic properties the end products produced by the use of the claimed intermediates might have, nor could they predict that they would possess any at all. * * *

Appellants, however, also urge that their intermediates are "useful" substances even under the Patent Office interpretation of Nelson. They contend that the 6-methyl aromatic steroids produced from their claimed compounds *are* members of a class of aromatic estrogen compounds, some of which are useful commercially. They refer specifically to certain members of that class in their brief. But appellants have not disclosed or otherwise shown that *any* 6-methyl aromatic steroid which can be produced from their intermediates possesses activities in common with those commercial members of the aromatic steroid series. We cannot accept their arguments for reasons given under Part I of this opinion.

Footnote 10. In a footnote to the above comments, the Court added, 148 USPQ at 694 :

> Thus, in Application of Wilke, 50 CCPA 964, 314 F. 2d 558, 136 USPQ 435 , the court reversed a Patent Office denial of a process claim, holding that 35 U.S.C. § 112 (1964 ed.) was satisfied even though the specification recited only the manner in which the process was to be used and not any use for the products thereby yielded. See also Application of Adams, 50 CCPA 1185, 316 F. 2d 476, 137 USPQ 333
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> In Application of Szwarc, 50 CCPA 1571, 319 F. 2d 277, 138 USPQ 208 , *the court acknowledged* that *its view of the law respecting utility of chemical processes had changed since Bremner.* * * * (Emphasis supplied)

Footnote 11. It does not appear that appellants seriously disagree with us on the matter, for in their memorandum on reargument they state:

C. By analogy between a process for production of a product and an intermediate for producing an end product, such intermediate would not be useful within the meaning of 35 U.S.C. 101 merely because it can be used to make the intended product, or because the end product belongs to a class of compounds now the subject of serious scientific investigation.

Dissenting Opinion Text

Dissent By:
Rich, Judge.

Notice of Forthcoming Dissenting Opinion **

I, like Judge Smith, whose sentiments I share, am now revising a dissenting opinion to cover this case and the companion Joly case (No. 7472), 153 USPQ 45 , argued together December 5, 1966, and involving similar issues. I initially filed my tentative dissenting opinion herein February 1 in response to the December 22 majority opinion and a January 24 opinion in Joly. Thereafter the majority opinion in Joly was 75% rewritten on February 8 and again, on February 20, its content, responsive in part to observations in my dissent, was reduced 50%. In the ensuing three weeks the court has conferred on a long agenda of cases and held a week of hearings March 6-10 , upon the conclusion of which I resumed, on March 13, my revision of the dissent. On that day notice was given by the Chief Judge that these two cases "will go down Thursday, March 16."

Protest to the arbitrary use of assumed power having proved futile, this unprecedented display of unseemly haste, condoned by the majority, necessitates this notice.

Footnotes

Footnote ** Editor's Note: See 153 USPQ 266 for dissenting opinions filed Apr. 10, 1967.

Dissenting Opinion Text

Dissent By:
Smith, Judge, dissenting.

Our usual practice is to release the majority opinion simultaneously with any dissenting opinions. There has been an unwarranted departure from this procedure in this case, the effect of which is to preclude an expression of my views at this time. I am unable to

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see wherein the cause of justice is served by such an irregular procedure. This dissent is therefore 1) a protest to the procedure here adopted, and 2) a notice that my full written dissent will be forthcoming as soon as the pressures of court work permit.

Concurring Opinion Text

Concur By:

Worley, Chief Judge, specially concurring.

It is most regrettable that for the first time in the history of this court, the usual orderly processes of the court have been ignored by a minority.

The instant appeal was *re-argued* December 5, 1966. The majority opinion was circulated December 22 in its present form. Yet, now, nearly three months later, the dissenting opinions are not available and no valid excuse is given.

It would seem that if the majority can direct its time and attention to expediting the work of the court it should not be too much to expect the same diligence from the minority.

It should not be necessary to say that the duty of this court is to the litigants, applicants for patents, the Patent Office and the public-not to the possible whims and caprices of individual judges. It is impossible to discharge that duty by condoning the instant derelictions, which hereafter will not be countenanced.

Footnote * Senior District Judge, Eastern District of Pennsylvania, sitting by designation.

- End of Case -